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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/625,024	07/22/2003	Tomio Kimura	03350CIP/HG	9538

1933 7590 07/13/2005

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EXAMINER	
HUANG, EVELYN MEI	

ART UNIT	PAPER NUMBER
1625	

DATE MAILED: 07/13/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/625,024	KIMURA ET AL.	
	Examiner	Art Unit	
	Evelyn Huang	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 April 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,14,16,37-64,70 and 71* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1,14,16,37-49,70 and 71* is/are allowed.

6)☒ Claim(s) *50-64* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1, 14, 16, 37-64, 70, 71 are pending. Claims 2-13, 15, 17-36, 65-69 have been canceled according to the amendment filed on 4-21-2005.

Election/Restrictions

2. In response to the restriction requirement mailed on 10-19-2004, Applicant has elected with traverse the invention of Group I, claims 24, 36-46, and claims 1-23, 25-35, 47-49 in part. The species elected is the compound of claim 41.

Applicants have requested rejoining the method claims 50-64 upon allowance of the compound claims. Accordingly, these claims are rejoined.

Inventorship

3. In view of the papers filed on 4-21-2005, the inventorship in this nonprovisional application has been changed by the deletion of Kazumasa Aoki.

The application will be forwarded to the Office of Initial Patent Examination (OIPE) for issuance of a corrected filing receipt, and correction of Office records to reflect the inventorship as corrected.

Claim Rejections - 35 USC § 112

4. The rejection for Claims 1-49 under 35 U.S.C. 112, second paragraph, is withdrawn in view of the amendment obviating the rejection.

Claim Rejections - 35 USC § 112

5. The scope enablement rejection for Claims 1-30, 32-36, 48, under 35 U.S.C. 112, first paragraph, is withdrawn in view of the amendment incorporating the allowable claim 31 into the

claims. The scope of the amended claims is now commensurate with that of the objective enablement.

Claim Objections

6. The objection of Claims 1-23, 25-35, 47-49 for containing non-elected subject matter is withdrawn in view of the amendment deleting the non-elected subject matter from the claims.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 50-64 are rejected under 35 U.S.C. 112, first paragraph, because the specification, is only enabling for using the inventive compound for the inhibition of IL-1β and TNFα production, thereby useful for the treatment of inflammation, rheumatoid arthritis or osteroarthritis. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

a. *Nature of the invention.*

The instant invention is drawn to a compound with inhibitory activity against the production of inflammatory cytokines for the treatment or prophylaxis of diseases where inflammatory cytokines are involved, such as pain/inflammation, rheumatoid arthritis, osteroarthritis or septicemia.

b. *State of the prior art and Predictability/unpredictability of the art.*

Cytokines, including interferons, tumor necrosis factor, interleukins, chemokines, colony stimulating factors and transforming growth factors, play a variety of roles in host defense and normal and abnormal homeostatic mechanisms (Cohen et al. American Journal of Clinical Pathology (1996), 105(5) : 589-598, abstract). A dynamic and ever shifting balance exists

between the proinflammatory cytokines and the anti-inflammatory components of the human immune system. All the anti-inflammatory cytokines have at least some proinflammatory properties as well. The net effect of any cytokine is dependent on the timing of the cytokine release, the local milieu in which it acts, the presence of competing or synergistic element, cytokine receptor density, and tissue responsiveness to the particular cytokine (Steven et al. Chest (2000), 117(4): 1162-1172, page 1162, second paragraph). For example, IL-6, although it has been regarded as a proinflammatory cytokine (as recited in "Background of the Invention" in the specification), it has been shown to inhibit the production of proinflammatory cytockines, such as GM-CSF, IFN-alpha, MIP-2, and has been placed as an anti-inflammatory cytokine group (Steven et al. page 1165).

At the time of the invention, the nexus between the inhibition of IL-1β and TNFα production and the treatment or prophylaxis of pain or septicemia has not been predictably established. The criteria for determining the subject susceptible to the diseases wherein inflammatory cytokines are involved have not been fully determined to allow for the prevention/prophylaxis of these diseases.

The high degree of unpredictability is well recognized in the cytokine art. A slight change in the structure of the compound would drastically change its biological activity in vitro. In the in vivo system, the degree of unpredictability multiplies in view of the complexity under physiological conditions as discussed in the paragraph above.

c. *Amount of guidance/working examples.*

The preparation of example compounds has been described.

The procedures for assessing the ability of the example compounds to inhibit IL-1β and TNFα production in human blood cells are described in Test Example 1, the results are shown for compound of Example 2 and 12. Test Examples 2-6 also describe the in vivo procedures for inhibition of IL-1β and TNFα production, the in vivo procedures for measuring the activity in preventing the development of arthritis in rats and mice, and in treating arthritis in mice. Results for the in vivo procedures are not shown.

d. *Breadth of the claims.*

Applicant's assertion that all the inventive compound would be effective inhibitors of any proinflammatory cytokines (including GM-CSF, IFN-alpha, MIP-2 etc., and the anti-inflammatory cyctokines which may act as proinflammatory cytokines, such as IL-6), thereby useful in treating or ***prophylaxis*** of all the diseases involving the inflammatory cytokines does not commensurate with the scope of the objective enablement, especially in view of the high degree of unpredictability in the cytokine art and the working examples limiting only to inhibition of the production of IL-1β and TNFα, (paragraphs b, c, above).

f. *Quantitation of undue experimentation.*

Since insufficient guidance and teaching have been provided by the specification (paragraphs c-e above), one of ordinary skill in the art, even with high level of skill, is unable to use the instant compound as claimed without undue experimentation except for using the inventive compounds for treatment of inflammation, rheumatoid arthritis or osteroarthritis.

Allowable Subject Matter

8. Claims 1, 14, 16, 37-49, 70, 71 are allowed.

Anantanarayan (WO 00/31063, PTO-1449) discloses a p38 kinase inhibiting pyrazolyl compound. The closest prior art compounds (pages 390-391, Example A-388, 389; page 1157) has a monocyclic nitrogen containing moiety instead of the instant bi- or tricyclic nitrogen containing moiety of formula IIa, IIb or IIc as R3. Absent is the motivation to modify the prior art compound to arrive at the instant invention.

Conclusion

9. THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

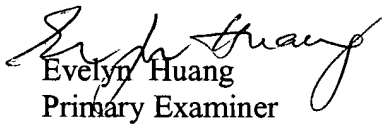
A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Evelyn Huang whose telephone number is 571-272-0686. The examiner can normally be reached on Tuesday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Evelyn Huang
Primary Examiner
Art Unit 1625